REMARKS

Claims 1-21, 23, and 25-32 are pending in the application, with Claims 1, 12, 21, 23, 25, 28 and 31 amended in this paper. The amendments to the claims find support in the specification and claims as originally filed. For example the amendments to Claims 1, 12, 21, 25 and 31 regarding peptide nucleic acids of about 25 to about 70 bases in length tethered to a microarray surface, and related microarrays, find support in the specification and claims as originally filed, for example, at page 8, line 22, page 9, lines 10-11, and page 16, line 11, and elsewhere in the application as filed. The amendments to Claims 23, 28, 29 and 30 regarding proteomic chips find support in the specification and claims as originally filed, for example, at page 5, lines 26-27; at page 6, lines 20-21; page 9, lines 15-20; at page 12, lines 5-13; page 14, lines 27-28; and elsewhere in the application as filed. No new matter is added by way of the claim amendments.

Claims 1-21, 25-27 and 31-32 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, with regard to Claims 1, 21, 25 and 31, and their dependent Claims 2-20, 26, 27, and 32, the Examiner suggests that the scope of the phrase "about 25 to about 70" is unclear. In addition, the Examiner suggests that the phrase "and/or" renders Claim 31 indefinite.

Claims 1-21, 23, and 25-32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Caple et al. (WO 99/04043, hereafter "Caple") in view of Kuga et al. (hereafter "Kuga").

Applicants traverse the claim rejections as discussed below.

The Rejections of Claims 1-21, 25-27 and 31-32 under 35 U.S.C. §112, Second Paragraph

Claims 1-21, 25-27 and 31-32 stand rejected as allegedly indefinite under 35 U.S.C. §112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to Claims 1, Claim 21, 25 and 31, and their dependent Claims 2-20, 26, 27, and 32, the Examiner has objected to the phrase "about 25 to about 70" as allegedly unclear.

Applicants note that claims directed to a range may include the word "about" and may include "about" at either, or at both, ends of the range. For example, M.P.E.P. at 2173.05(b)(A) discusses the term "about" and notes that claims including the term "about" have been held to be definite (citing, *e.g., Ex Parte Eastwood*, 163 USPQ 316 (Bd. App. 1978) and *W.L. Gore & Associates, inc. v. Garlock, Inc.* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)). In addition, applicants note, for example, that similar claims have been allowed by the USPTO. For example, the claims of U.S. Patent No. 6,235,493 illustrate allowed claims including the term "about"; *e.g.,* Claim 2 of U.S. Patent No. 6,235,493 is: "The method of Claim 1 wherein the amino acid sequences X and Y are independently between about 1 and about 10,000 amino acids."). Accordingly, applicants respectfully submit that these claims are not indefinite, and that the rejection of Claims 1-21, 25-27 and 31-32 as allegedly unclear are overcome.

The Examiner has suggested that the phrase "and/or" renders Claim 31 indefinite. However, as amended, Claim 31 no longer includes the phrase "and/or" so that the rejection of Claim 31 under 35 U.S.C. §112, second paragraph, is believed to be moot.

Thus, applicants respectfully submit that Claims 1-21, 25-27 and 31-32 are not indefinite. Accordingly, applicants respectfully submit that the rejections of Claims 1-21, 25-27 and 31-32 under 35 U.S.C. §112, Second Paragraph, are overcome.

The Rejections Under 35 U.S.C. §103(a)

Claims 1-21, 23, and 25-32 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Caple et al. (WO 99/04043, hereafter "Caple") in view of Kuga et al. (hereafter "Kuga").

In order to establish a prima facie case of obviousness, there must be: 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art,

and not based on the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Peptide Nucleic Acid Microarray Claims

Claims 1-21, and 25-27 are directed to systems and methods which require, among many other elements, the elements of a microarray comprising peptide nucleic acid (PNA) probes comprising about 25 to about 70 bases in length tethered to a microarray surface.

Applicants note that a peptide nucleic acid (PNA) molecule is chemically and structurally different than a DNA molecule. These differences are illustrated in the figure below (Figure 1 from Ray and Norden, *FASEB J.* **14**:1041-1060 (2000):

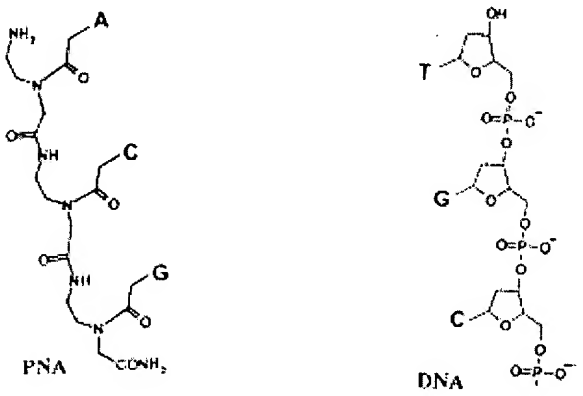


Figure 1. Chemical structure of PNA (left) and DNA (right).

Note that PNA molecules, as shown on the left, have a *peptide* backbone, while DNA molecules (shown on the right) have a backbone of *sugar molecules* linked together by phosphates. Other chemical differences may also be apparent. The letters A, T, G and C represent the bases adenine, thymine, guanine and cytosine in the illustrations of both PNA and DNA strands. It is the presence of these bases that allows PNA to selectively bind to target DNA or RNA molecules. However, as is made clear by the illustration, PNA molecules are significantly different than DNA molecules, and have

different properties as well (being more resistant to degradation by nucleases than DNA, for example). More background information regarding PNA molecules and regarding the differences between PNA and DNA molecules is found in the article from which the iliustration (above) was taken; a copy of that article is provided with this response.

Applicants note that Caple and Kuga fail to discuss or suggest PNA molecules or their uses. In fact, Caple mentions only DNA (*e.g.,* page 10, line 19) and not PNA. A word search of the text of Kuga shows that the words "peptide nucleic acid" and the acronym "PNA" do not appear in Kuga. The Examiner's suggestion (page 6, lines 5-6) that Kuga provides "hybridization information collected from array comprising peptide nucleic acid probes" is incorrect.

Kuga make clear that their methods are directed to DNA molecules. For example, Kuga state that they "have developed high-density cDNA filter analysis (referred to as "HDCFA" hereinafter) which enables the simple analysis of the expression levels of a vast amount of genes ... by recovering thereafter a DNA having a complementary sequence to the RNA strand of the mRNA, the present invention has been compieted. " (Kuga, col. 2, lines 18-28). Further discussion of the requirement for DNA in the methods of Kuga may be found, for example, at col. 3, lines 36-48; at col. 5, lines 20-24 and lines 25-36; and at col 10, lines 50-65 of Kuga. Thus, the method of Kuga requires recovery of a cDNA of the complementary mRNA, and, rather than discussing or suggesting the use of PNA probes or PNA microarrays, actually teaches away from the present invention by requiring cDNA molecules unlike the PNA molecules of Claims 1-21, and 25-27.

Thus, Applicants note that neither of the cited references discuss or suggest PNA molecules, or PNA microarrays, or the use of PNA molecules in any manner. As acknowledged by the Examiner (see, *e.g.,* page 5, lines 16-22), Caple does not disclose this element of the claimed invention, among many other elements lacking from Caple. In view of the well-known differences between PNA and DNA, it is evident that the Examiner's comment on page 5, line 21-22 to page 6, line 1 that "even though Caple does point out at page 10, line 19, stored data in database can be DNA data or

sequence listing" does not address the differences between the claimed invention and Caple. Kuga also fails completely to make up this lack, failing to include any reference to PNA molecules, PNA microarrays, or their uses.

Moreover, neither Caple nor Kuga, nor the combination of Caple with Kuga, provide systems or methods comprising a PNA microarray. Thus, the combination of Caple with Kuga fails to make obvious the claimed invention.

In addition, neither Caple nor Kuga, nor Caple together with Kuga, provide or suggest the element of a PNA probe comprising about 25 to about 70 bases in length tethered to a microarray surface. Caple and Kuga together not only fail to provide or suggest a PNA probe and a PNA microarray, they also fail to provide or suggest a PNA probe that is tethered to a microarray surface. Caple combined with Kuga fails to provide a tethered probe; fails to provide a tethered PNA probe; fails to provide a PNA probe having a length of about 25 to about 70 bases; and fails to provide a microarray comprising such tethered PNA probes. Accordingly, Caple combined with Kuga fails to make obvious these claim elements as well.

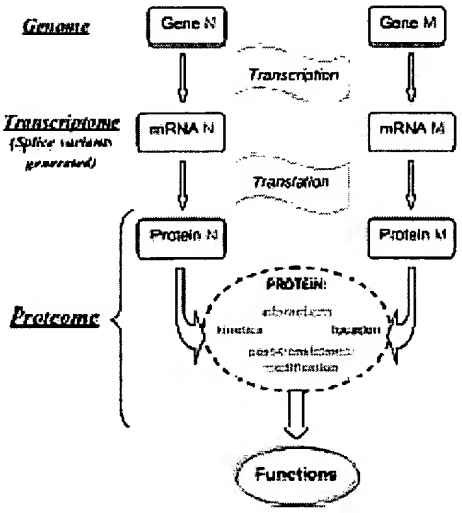
Caple and Kuga also fail to provide other claim elements; for example, Caple combined with Kuga fail to provide or suggest methods comprising updating hybridization parameters and profiles. Neither Caple nor Kuga provide methods for diagnosing a physiological condition and recommending treatment comprising collecting information from a PNA microarray wherein the methods comprise analyzing data using artificial intelligence comprising application of a rate algorithm adapted to detect changes between compared parameters and a profile, and updating stored parameters and profiles. Caple and Kuga also fail to provide, or to suggest providing, these elements discussed above in combination with the many other elements of Claims 1-21, and 25-27.

Moreover, neither Caple nor Kuga suggest or motivate one to combine Caple with Kuga in order to provide the missing elements of the claimed invention. Thus, the cited references do not provide any suggestion to be combined to provide the claimed invention. Since the references fail to provide or suggest the missing elements, even if one were to combine the references despite the lack of motivation to do so, the

combination of Cable and Kuga would fail to provide any reasonable expectation of success for such a combination of elements. Accordingly, Applicants submit that the rejection of Claims 1-21, and 25-27 directed to systems and methods comprising a microarray comprising PNA probes comprising about 25 to about 70 bases in length tethered to a microarray surface are overcome.

Proteomics Claims

Claims 23 and 28-30 are directed tc methods for diagnosing a physiological condition comprising the use of a proteomics chip. A proteomics chip differs from a PNA chip and from any sort of genomic analysis device in that it provides information regarding the *proteins* present in a sample, and not the genetic material which codes for the proteins. These points are discussed in the article "Proteomics techniques and their application to hematology" (*Blood* **103(10)**:3624-3634 (2004)), a copy of which is enclosed. As discussed in that paper, different sorts of information are available from different molecules present in a biological sample. For example, *genomic* information is different than *proteomic* information, genomic information dealing with the genetic makeup of the cells in a sample and of the genes expressed in those cells, while proteomic information deals with the proteins found in that sample, after any splicing, chemical modification, aggregation, or other actions that might affect those proteins has occurred. This is illustrated in Figure 1 of that paper:



The upper boxes in the figure above represent the genomic level: the DNA of a cell that encodes its full complement of genes. The boxes the next level down represent the RNA copies of those genes that are transcribed in this particular cell (not all genes being active in a particular cell at any one time). It is from these RNA molecules that cDNA copies are made. The third, and lowest level of boxes represents those mature proteins present in the cell, after any modifications have been made to them to make them fully functional - the proteome. Proteomics devices and analysis are directed to this last level, as opposed to being directed to the other, upper levels depicted in the illustration.

Since only some of the proteins encoded by the genetic material present in a cell are actually made, and since proteins are often chemically altered after being made from the genetic material, and since proteins often aggregate or otherwise combine with other proteins to form functional units or systems, *proteomic* information differs from, and is more directly linked to the physiology of cells in a sample, than is *genomic* information. This may be particularly true in some disease states which affect cellular proteins without significantly affecting the genetic make-up of the cell. Thus, discussion of genomic methods is misdirected when applied to Claims 23 and 28-30 which deal with proteomics.

Claims 23, 28, 29, and 30 are directed to methods for diagnosing a physiological condition of an organism and for recommending treatment for said organism, the methods including a step of providing a proteomics chip comprising a substrate to which protein probes are bound, among other steps and elements. As discussed above, a proteomics chip differs from other devices such as cDNA arrays or even PNA microarrays in being directed to *proteins* and in providing information about the *proteome* as opposed to some other level of information. A proteomics chip is not a device that is used for, or that provides, DNA information.

Applicants note that neither Caple nor Kuga discuss or suggest proteomic devices, the gathering of proteomic information, nor the use of proteomic devices in any methods. In particular, Caple and Kuga each fail to discuss using a proteomics device

in methods for diagnosing a physiological condition of an organism and for recommending treatment for said organism.

As discussed above, Caple and Kuga also fail to provide other claim elements, such as, for example, failing to provide or suggest methods comprising updating hybridization parameters and profiles, and failing to provide such elements in combination with the many other elements of Claims 23 and 28-30. Neither Caple nor Kuga provide methods for diagnosing a physiological condition and recommending treatment comprising collecting information from a proteomics chip wherein the methods comprise analyzing data using artificial intelligence comprising application of a rate algorithm adapted to detect changes between compared parameters and a profile, and updating stored parameters and profiles.

Moreover, neither Caple nor Kuga suggest or motivate one to combine Caple with Kuga in order to provide the missing elements, including but not limited to failing to suggest or motivate providing a proteomics chip. In addition, the references failing to provide or suggest the missing elements, they also fail to provide any reasonable expectation of success for such a combination. Accordingly, Applicants submit that the rejection of Claims 23 and 28-30 are overcome.

Claims 31 and 32

Similarly, neither Caple nor Kuga provide methods for diagnosing a physiological condition and recommending treatment comprising collecting information from a microarray having either PNA probes or oligonucleotide probes wherein the methods comprise analyzing data using artificial intelligence comprising application of a rate algorithm adapted to detect changes between compared parameters and a profile, and updating stored parameters and profiles. However, Claims 31 and 32 include such elements, among many other elements. Neither Caple nor Kuga suggest such elements, nor suggest that Caple and Kuga could be or should be combined to provide such elements. Caple and Kuga also fail to provide, or to suggest providing, these elements in combination with the many other elements of Claims 31 and 32. Failing to provide or suggest these elements, the combination of Cable and Kuga together also

fails to provide any reasonable expectation of success for such a combination of elements. Thus, the cited references fail to make Claims 31 and 32 obvious.

Comments on Other Elements

Applicants submit that discussion above, noting some of the elements lacking from the combination of the cited references, overcomes the rejections of Claims 1-21, 23, and 25-32. However, applicants further provide the following comments with regard to statements made by the Examiner in the Office action mailed February 3, 2005.

Applicants note that the Examiner acknowledges that Kuga does not teach the claim element of probes comprising about 25 to about 70 bases in length tethered to a microarray surface (page 6, lines 7-8). However, the Examiner suggests (page 6, lines 12-13) that "the length of the probes tethered to a microarray surface" is "a matter of obvious design choice" without any supporting reference to indicate why he believes this to be so. Applicants respectfully submit that in view of the lack of teaching of this claim element by the cited references, and in the absence of any reference to suggest it might be obvious, that claim rejections relying on this claim element being obvious are overcome.

Although the Examiner suggests that Caple "teaches using DNA sequences to find treatment for Alzheimer's disease" (page 6, lines 19-20) no such teaching is found in Caple, although Caple does mention cognitive testing on page 6, line 21. However, cognitive testing does not involve the use of DNA sequences.

Referring to Claim 2, the Examiner suggests that Caple teaches data comprising "genetic pattern database data for chip ID" (page 7, lines 7-8) yet provides no citation for this teaching. Applicants have not been able to identify any such teaching in Caple.

Referring to Claims 1 and 8, the Examiner suggests that Caple provides encryption (page 4, lines 24-25 and page 8, lines 5-6), suggesting that "any communication within a network contains basic encryption." However, despite the Examiner's comment, it is clear that Caple does not discuss or suggest encryption. Applicants submit that encryption, like all other claim elements, must be discussed in a reference in order to be provided by that reference. The cited references lacking any

discussion of encryption, Applicants respectfully submit that the cited references fail to make obvious Claim 8.

Applicants note that the cited references fail to discuss PNA or proteomics. Thus, the Examiner's suggestion (page 9, lines 14-15 and page 10, line 13) in referring to Claims 16 and 21 that Caple and Kuga teach "hybridization information" is not directed to the present claims, since the cited references do not discuss or suggest hybridization to PNA or proteomic microarrays.

The Examiner cites the phrase "sequence listings" from page 10, line 19 of Caple to suggest that the cited references provide "genetic pattern processing" (page 9, line 21, referring to Claim 17). However, a sequence listing is known by one of ordinary skill in the art to be a listing, in order, of the nucleotides (for a nucleic acid molecule) or amino acids (for a protein) that make up a nucleic acid or protein. Sequence listings are used to identify and characterize a molecule. A pattern of genetic material (such as many nucleic acids present in a sample) would be needed for "genetic pattern processing." As these terms are used in the art, applicants respectfully submit that mere sequence listings do not provide "genetic pattern processing."

With regard to Claim 23, the Examiner (page 10, lines 20-21) notes that Kuga at column 3, line 45 discusses cDNA probes; however, the Examiner seems to imply that a discussion of cDNA probes might be relevant to the claim element "proteomics chip." However, as discussed above, a proteomics chip differs in significant ways from a cDNA probe, and discussion of a cDNA in no way makes obvious the claim element "proteomics chip."

With regard to Claims 23, the Examiner cites Kuga at column 6, lines 5-9 to suggest that "a routine nucleotide sequencing method" is a rate algorithm (page 11, lines 2-3). It is unclear how a methods for determining the identifying chemical characteristics of a nucleic acid molecule could be the claimed rate algorithm. As discussed in the specification of the present application (page 20, lines 26-27) the "rate algorithm allows for fast pattern matching in large rule set(s) by storing information about the rules in a network." Applicants respectfully submit that neither Caple nor

Kuga, nor the combination of the two, provide a rate algorithm, and that this claim element is not made obvious by the cited references.

Accordingly, Applicants believe that the claims are not obvious over the cited references, that the combination of Caple and Kuga together fails to provide all missing elements of Claims 1-21, 23, and 25-32 and respectfully submits that the rejection of Claims 1-21, 23 and 25-32 under 35 U.S.C. §103(a) is overcome.

CONCLUSION

Applicants respectfully requests consideration and allowance of all pending claims. The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **25527-0005**.

Respectfully submitted,

Date: May 2, 2005

By: _____
James A. Fox (Reg. No. 38,455)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Direct Dial: (650) 324-6951
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2109643 v1
5/1/05 1:17 PM (25527.0005)